IFW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:

Hiroshi TOMIYAMA, et al.

Serial No.: 10/560,357 Group: 1623

Filed: December 12, 2005 Examiner: L. D. Bland

FOR: SERUM CHOLESTEROL LOWERING AGENT OR PREVENTIVE OR THERAPEUTIC AGENT FOR ATHEROSCLEROSIS

Date: July 1, 2008
Atty. Docket: TAN-356

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

COMMUNICATION

Sir:

In the above-captioned application, an Amendment was filed on June 30, 2008, using Certificate of Mailing procedure. In the Remarks, the representation was made that accompanying the Amendment was an English translation of the Japanese language priority document along with the translator's verification. Inadvertently, these documents were not submitted with the Amendment. Please find submitted herewith the English

translation of JP 2003-185171 along with the verifying declaration of the translator.

Respectfully submitted,

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IN THE MATTER OF AN APPLICATION FOR LETTER PATENT
BY KOTOBUKI PHARMACEUTICAL CO., LTD.

I, Kazuhiro Kosakai, a translator residing at 1054-7, Hoya, Ueda-shi, Nagano, 386-1321 Japan, am well acquainted with the Japanese and English languages and hereby certify that to the best of my knowledge and belief, the following is a true translation into English made by me of the document filed by Kotobuki Pharmaceutical Co., Ltd., with the Japanese Patent Office JPA No.2003-185171 filed on June 27, 2003 for letter Patent.

Dated this June 2, 2008

Kazuhiro Kosakai

[Name of Document]	PETITION OF PATENT
[Reference Number]	P 150073(JPA No.2003-185171)
[To]	Sinnichiro Ohta The Director-General, Patent Office
[IPC]	A61K 31/395
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[List number of Prepaid]	024040
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[Name] Specification	1

[Name]	Abstract	1
[Yes or No of Proof]		Yes

Specification

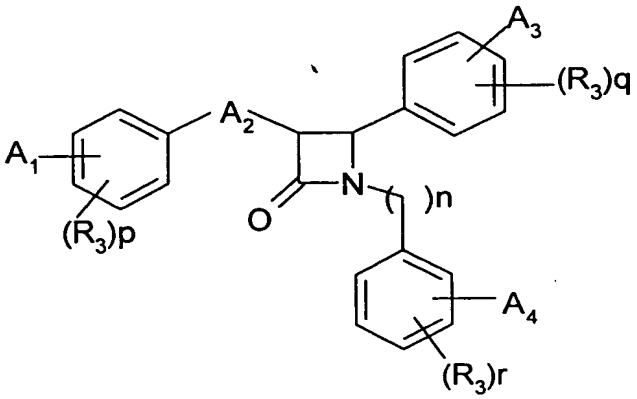
[Title of the invention]

Serum cholesterol lowering agents or preventive or therapeutic agents for atherosclerosis

[Range of the patent claim]

[Claim 1] Serum cholesterol lowering agents or preventive or therapeutic agents for atherosclerosis consist of the combination of a compound represented by the following general formula (I) or pharmaceutical acceptable salts and cholesterol biosynthesis inhibitors and/or fibrate-type cholesterol lowering agents.

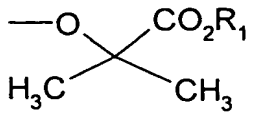
[Compound 1]



---------- (I)

[wherein : A_1, A_3 and A_4 are hydrogen atom, halogen atom, alkyl group having one to five carbon atoms, alkoxy group having one to five carbon atoms, $-COOR_1$, a following formula :

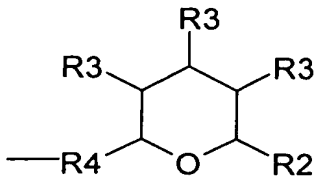
[Compound 2]



---------- (b)

(wherein : R_1 is hydrogen atom or alkyl group having one to five carbon atoms) or a following formula :

[Compound 3]



---------- (a)

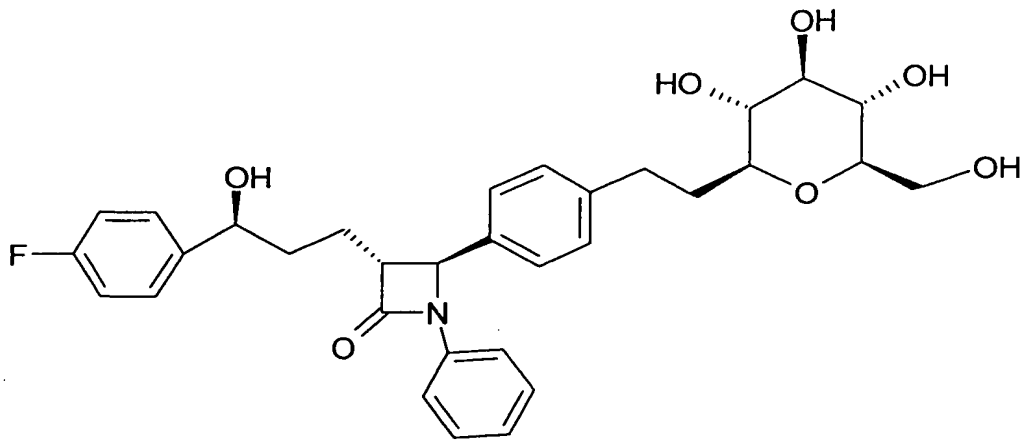
[wherein : R_2 is $-CH_2OH$ group, $-CH_2OC(O)-R_1$ group or $-CO_2-R_1$ group ; R_3 is –OH group or $-OC(O)-R_1$ group ; R_4 is $-(CH_2)_kR_5(CH_2)_l-$ (k and l are 0 or 1 more integer ; k + l is 10 or fewer integer). R_5 means single bond (-), -CH=CH-, $-OCH_2-$, -NH-, $-S(O)_m-$ (m are 0, 1 or 2), carbonyl group or –CH(OH)-.] More than one of A_1, A_3 and A_4 in formula (I) must be the group in above-mentioned formula (a). A_2 is alkyl chain having one to five carbon atoms, alkoxy chain having one to five carbon atoms, alkenyl chain having one to five carbon atoms, hydroxyl alkyl chain having one to five carbon atoms or carbonyl alkyl chain having one to five carbon atoms. n, p, q or r are 0, 1 or 2.]

[Claim 2] Serum cholesterol lowering agents or preventive or therapeutic agents for atherosclerosis described in claim 1 consist of the mixture of a compound represented by the above general formula (I) or pharmaceutical acceptable salts and cholesterol biosynthesis inhibitors and/or fibrate-type cholesterol lowering agents.

[Claim 3] Serum cholesterol lowering agents or preventive or therapeutic agents for atherosclerosis formed a kit by single packaging a container containing a compound represented by the above general formula (I) or pharmaceutical acceptable salts and a container containing cholesterol biosynthesis inhibitor and/or fibrate-type cholesterol lowering agents.

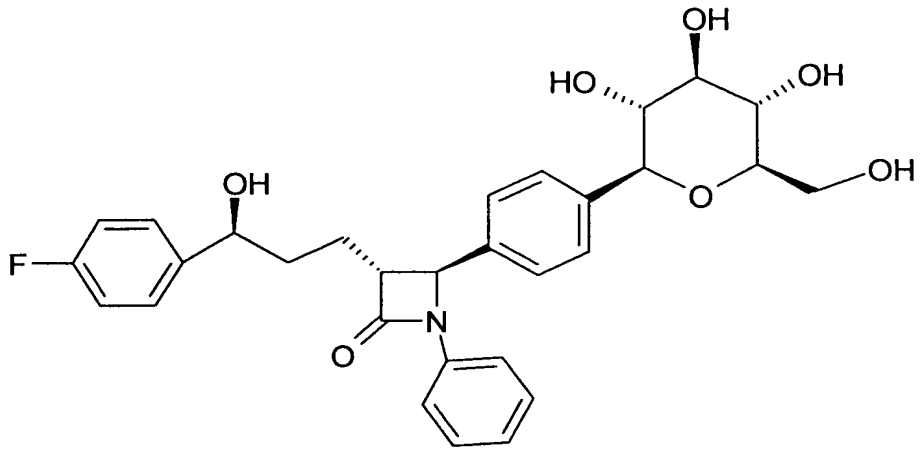
[Claim 4] Serum cholesterol lowering agents or preventive or therapeutic agents for atherosclerosis described in claim 1～3 consist of a compound which the above-mentioned general formula (I) is the following formula.

[Compound 4]



[Claim 5] Serum cholesterol lowering agents or preventive or therapeutic agents for atherosclerosis described in claim 1～3 consist of a compound which the above-mentioned general formula (I) is the following formula.

[Compound 5]



[Claim 6] Serum cholesterol lowering agents or preventive or therapeutic agents for atherosclerosis described in claim 1～5 characterized by the use of the cholesterol biosynthesis inhibitors which is at least one sort chosen from the group consist of HMG-CoA reductase inhibitors, squalene synthesis inhibitors and squalene epoxydase inhibitors.

[Claim 7] Serum cholesterol lowering agents or preventive or therapeutic agents for atherosclerosis described in claim 1～5 characterized by the use of fibrate-type cholesterol lowering agents which is at least one sort chosen from the group consisting of clofibrate, bezafibrate, simfibrate, fenofibrate, gemfibrozyl and AHL-157.

[Claim 8] A dosage method of serum cholesterol lowering agents or preventive or therapeutic agents for

atherosclerosis characterized by the administration of a compound represented by the above-mentioned formula (I) or pharmaceutical acceptable salts and cholesterol biosynthesis inhibitors and/or fibrate-type cholesterol lowering agents simultaneously or consecutively.

[Detailed description of the invention]

[0001]

[Technical field to which the invention pertains]

The present invention relates to medicinal compositions that are useful as serum cholesterol lowering agents or preventive or therapeutic agents for atherosclerosis, in more detail, relates to medicinal compositions of β-lactam cholesterol absorption inhibitors containing C-glycoside in those molecules combined with cholesterol biosynthesis inhibitors and/or fibrate-type cholesterol lowering agents.

[0002]

[Conventional technology]

Conventionally, cholesterol biosynthesis inhibitors or fibrate-type cholesterol lowering agents have been widely used for serum cholesterol reduction and prevention or therapy of atherosclerosis, and proposing the combination of β-lactam cholesterol absorption inhibitors and cholesterol biosynthesis inhibitors (Patent document 1). The present applicant has previously published that β-lactam cholesterol absorption inhibitors containing C-glycoside in those molecules have an excellent cholesterol lowering action, and are useful as serum cholesterol lowering agents (Patent document 2).

[0003]

[Patent document 1]

JP 8-505141

[Patent document 2]

WO-02/066464 A1

[0004]

[Problems to be solved by the invention]

The purpose of the present invention is supply of more excellent serum cholesterol lowering agents or preventive or therapeutic agents for atherosclerosis.

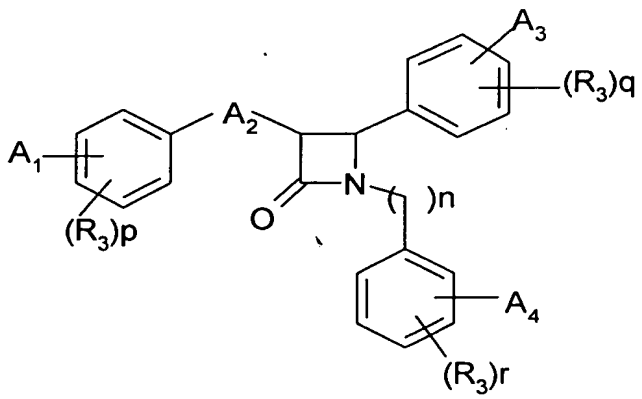
[0005]

[Means for solving problems]

The present invention is serum cholesterol lowering agents or preventive or therapeutic agents for atherosclerosis consist of the combination of a compound represented by the following general formula (I) or pharmaceutical acceptable salts and cholesterol biosynthesis inhibitors and/or fibrate-type cholesterol lowering agents.

[0006]

[compound 6]



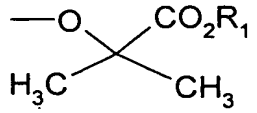
---------- (I)

[0007]

[wherein : A_1, A_3 and A_4 are hydrogen atom, halogen atom, alkyl group having one to five carbon atoms, alkoxy group having one to five carbon atoms, $-COOR_1$, a following formula :

[0008]

[compound 7]



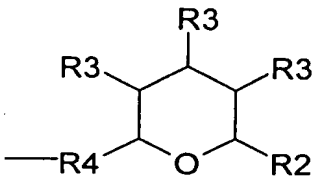
---------- (b)

[0009]

(wherein : R_1 is hydrogen atom or alkyl group having one to five carbon atoms) or a following formula :

[0010]

[compound 8]



---------- (a)

[0011]

[wherein : R_2 is –CH_2OH group, -$CH_2OC(O)$-R_1 group or -CO_2-R_1 group ; R_3 is –OH group or -$OC(O)$-R_1 group ; R_4 is -$(CH_2)_kR_5(CH_2)_l$- (k and l are 0 or l more integer ; k + l is 10 or fewer integer). R_5 means single bond (-), -CH=CH-, -OCH_2-, -NH-, -$S(O)_m$- (m are 0, 1 or 2), carbonyl group or –CH(OH)-.] More than one of A_1, A_3 and A_4 in formula (I) must be the group in above-mentioned formula (a). A_2 is alkyl chain having one to five carbon atoms, alkoxy chain having one to five carbon atoms, alkenyl chain having one to five carbon atoms, hydroxyl alkyl chain having one to five carbon atoms or carbonyl alkyl chain having one to five carbon atoms. n, p, q or r are 0, 1 or 2.]

[0012]

Also, the present invention is serum cholesterol lowering agents or preventive or therapeutic agents for atherosclerosis consist of the mixture of a compound represented by the above general formula (I) or pharmaceutical acceptable salts and cholesterol biosynthesis inhibitors and/or fibrate-type cholesterol lowering agents. Also, the present invention is serum cholesterol lowering agents or preventive or therapeutic agents for atherosclerosis formed a kit by single packaging a container containing a compound represented by the above general formula (I) or pharmaceutical acceptable salts and a container containing cholesterol biosynthesis inhibitor and/or fibrate-type cholesterol lowering agents. Also, it is able to administer a compound represented by the above general formula(I) or pharmaceutical acceptable salts and cholesterol biosynthesis inhibitors and/or fibrate-type cholesterol lowering agents simultaneously or consecutively.

[0013]

[Mode of carrying out the invention]

The present invention is serum cholesterol lowering agents or preventive or therapeutic agents for atherosclerosis consisting of the combination of a compound represented by the following general formula (I) or pharmaceutical acceptable salts and cholesterol biosynthesis inhibitors and/or fibrate-type cholesterol lowering agents. Concretely, this combined medicine means : ① the medicine combined a compound represented by the general formula (I) or pharmaceutical acceptable salts with cholesterol biosynthesis inhibitors, ② the medicine combined a compound

represented by the general formula (I) or pharmaceutical acceptable salts with fibrate-type cholesterol lowering agents, ③ the medicine combined a compound represented by the general formula (I) or pharmaceutical acceptable salts with cholesterol biosynthesis inhibitors and fibrate-type cholesterol lowering agents. This combined usage means combined administration, and is able to administer simultaneously or consecutively.

[0014]

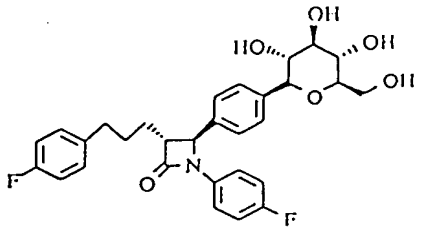
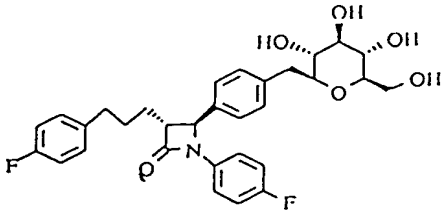
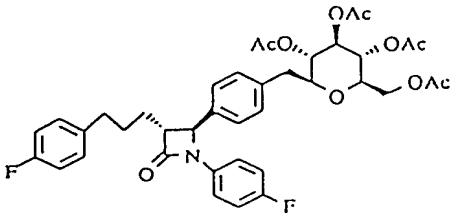
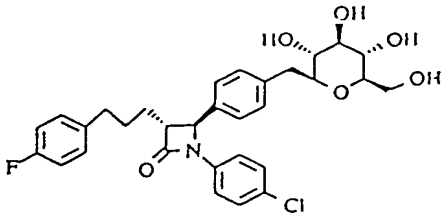
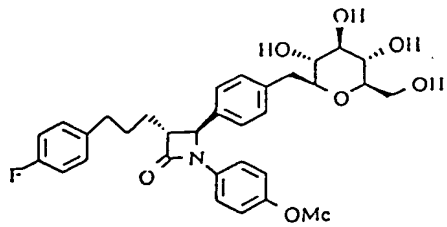
A compound represented by the above general formula (I) or pharmaceutical acceptable salts in the present invention have serum cholesterol lowering actions. These compounds are shown in patent document 2. These β-lactam compounds, which show cholesterol lowering actions and has C-glycoside in those molecules, show synergistic effects by using in combination with cholesterol biosynthesis inhibitors and/or fibrate-type cholesterol lowering agents for serum cholesterol lowering effect or preventive or therapeutic effect for atherosclerosis.

[0015]

A compound represented by the above general formula (I) or pharmaceutical acceptable salts using in the present invention are , for example, the compounds shown in Table 1～12.

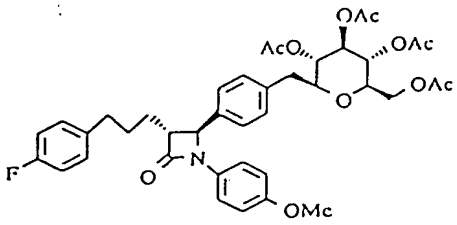
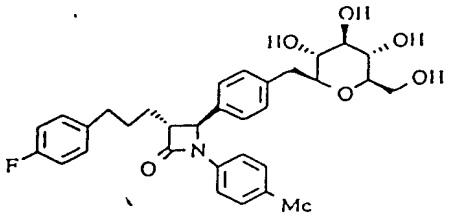
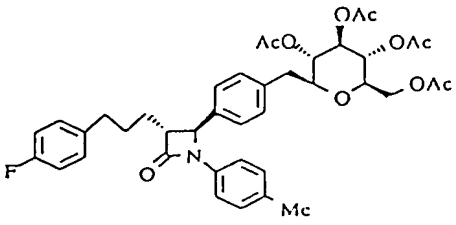
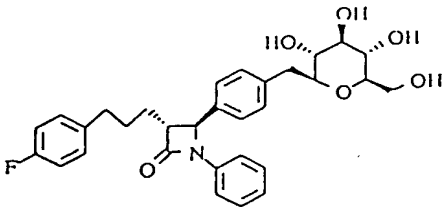
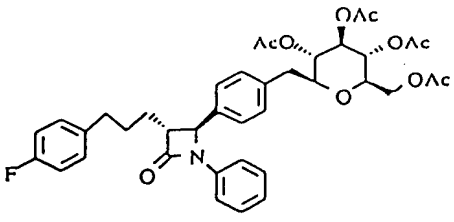
[0016]

[Table 1]

No.	Structure	mp (℃)	$[\alpha]_D^{25}$ / (C, Solv.)
1		89-90	-40.4 (C=0.5, MeOH)
2		110-112	-33.2 (C=0.5, MeOH)
3		56-58	
4		76-78	
5		73-75	

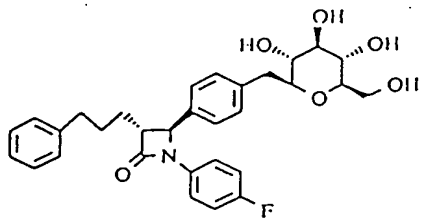
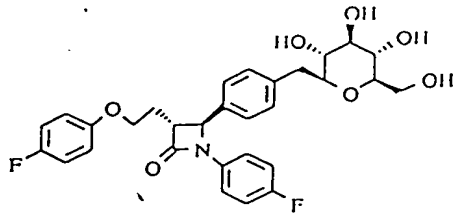
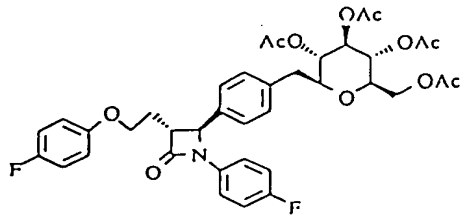
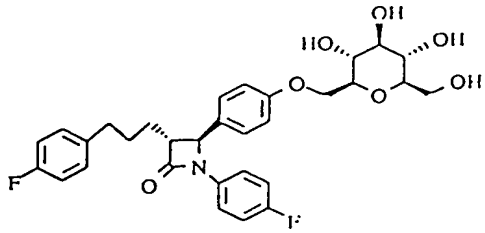
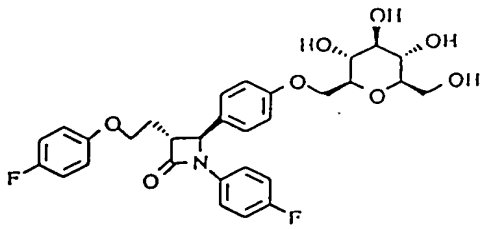
[0017]

[Table 2]

No.	Structure	mp (℃)	$[\alpha]_D^{25}$ / (C, Solv.)
6		60-62	
7		80-82	-46.7 (C=0.3, MeOH)
8		56-58	
9		84-86	-40.4 (C=0.5, MeOH)
10		60-61	

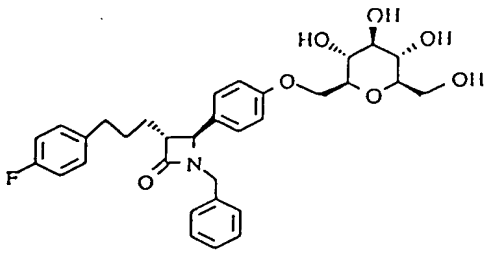
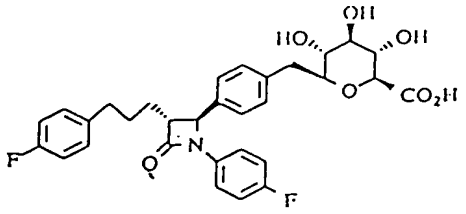
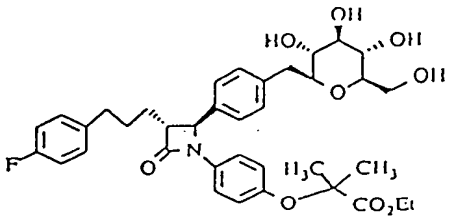
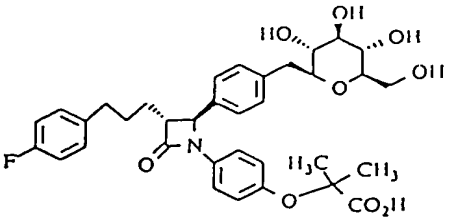
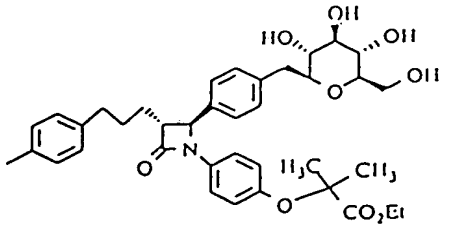
[0018]

[Table 3]

No.	Structure	mp (℃)	$[\alpha]_D^{25}$ / (C, Solv.)
11		74-75	
12		65-67	-40.4 (C=0.5, $CHCl_3$)
13		64-66	
14		61-62	
15		64-65	

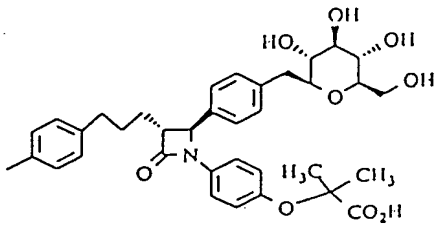
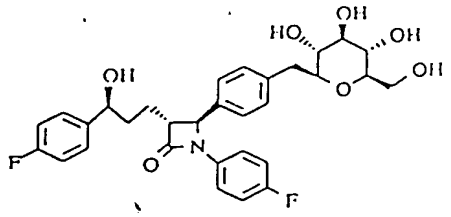
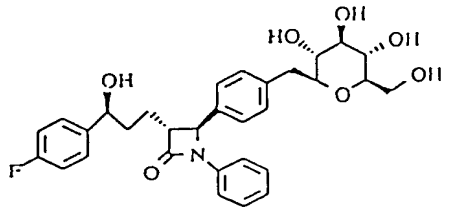
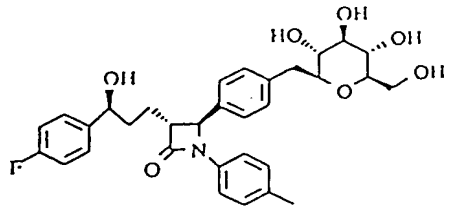
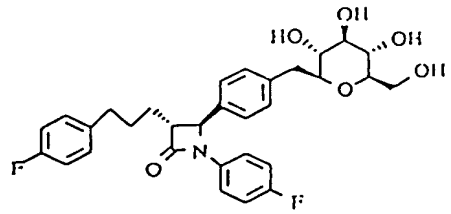
[0019]

[Table 4]

No.	Structure	mp (℃)	$[\alpha]_D^{25}$ / (C, Solv.)
16		73-75	
17		105-106	
18		73-74	
19		170-172	
20		76-78	

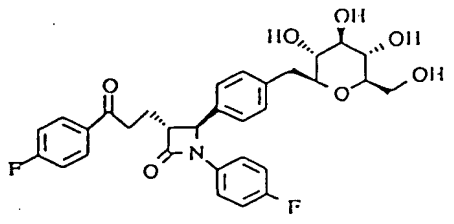
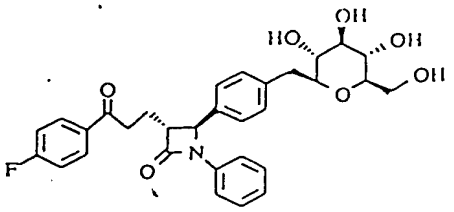
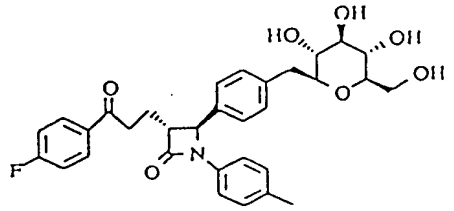
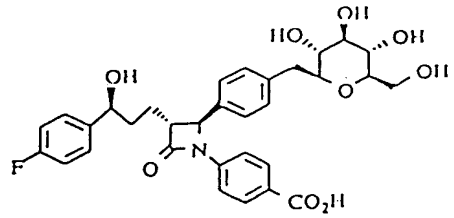
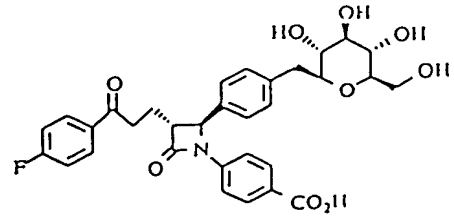
[0020]

[Table 5]

No.	Structure	mp (℃)	$[\alpha]_D^{25}$ / (C, Solv.)
21		161-162	
22		115-117	-71.3 (C=0.3, McOH)
23		104-106	-110 (C=0.5, McOH)
24		102-104	-58.0 (C=0.3, McOH)
25		67-69	-62.8 (C=0.5, McOH)

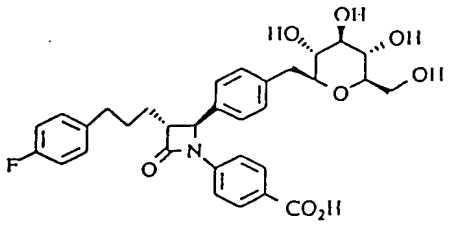
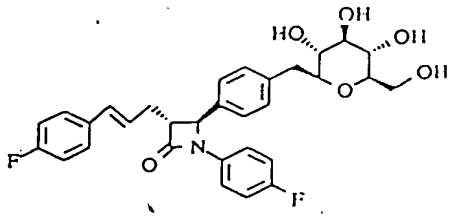
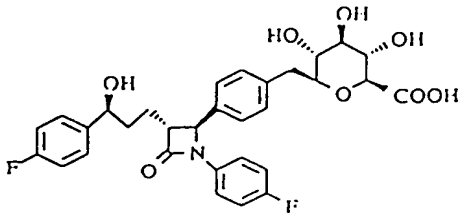
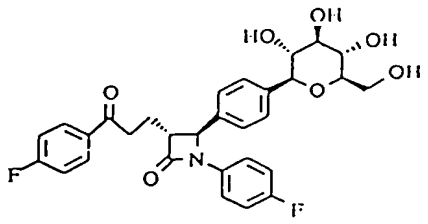
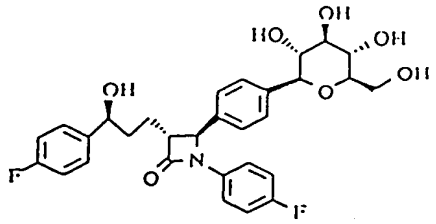
[0021]

[Table 6]

No.	Structure	mp (℃)	$[\alpha]_D^{25}$ / (C, Solv.)
26		78-80	-67.2 (C=0.5, MeOH)
27		104-106	-26.0 (C=0.5, MeOH)
28		86-88	-35.7 (C=0.6, MeOH)
29		148-150	-122.0 (C=0.3, MeOH)
30		102-104	-52.0 (C=0.3, MeOH)

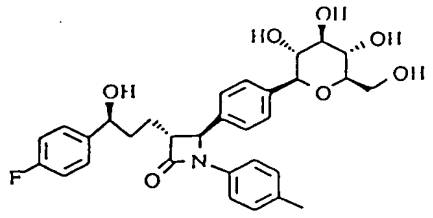
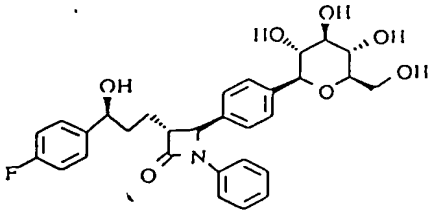
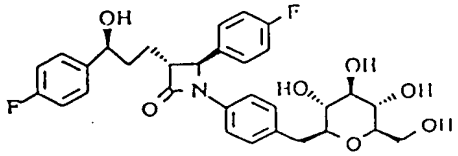
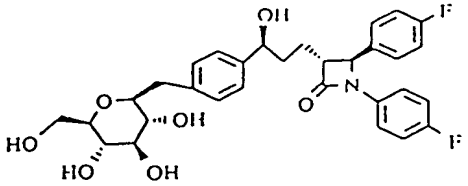
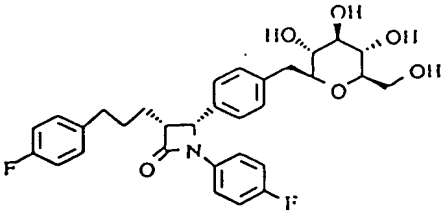
[0022]

[Table 7]

No.	Structure	mp (℃)	$[\alpha]_D^{25}$ / (C, Solv.)
31		97-99	
32		liq	-39.3 (C=0.8, MeOH)
33		82-84	-47.6 (C=0.5, MeOH)
34		83-85	
35		81-83	

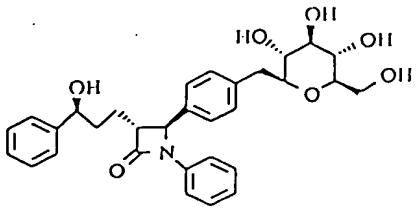
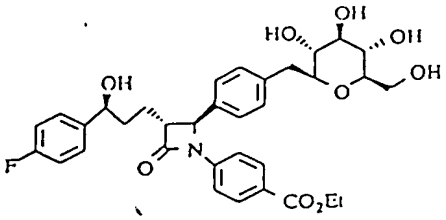
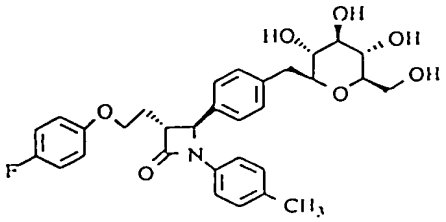
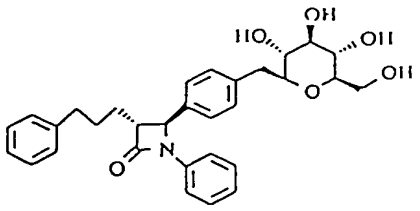
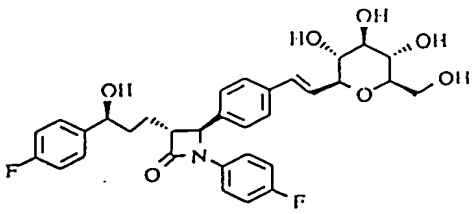
[0023]

[Table 8]

No.	Structure	mp (℃)	$[\alpha]_D^{25}$ / (C, Solv.)
36		79-81	
37		80-82	
38		200-201	-69.3 (C=0.3, MeOH)
39		126-128	-42.66 (C=0.3, MeOH)
40		78-80	

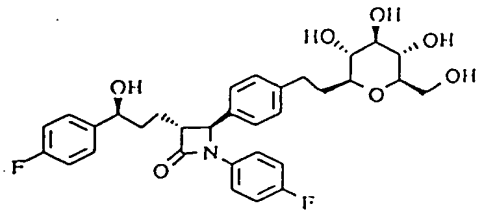
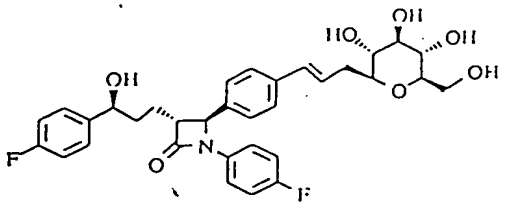
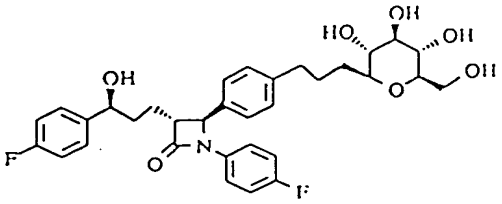
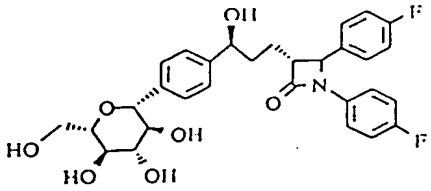
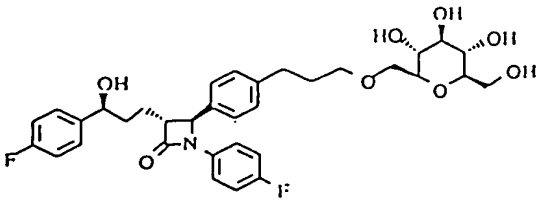
[0024]

[Table 9]

No.	Structure	mp (℃)	$[\alpha]_D^{25}$ / (C, Solv.)
41		110-112	-67.2 (C=0.5, MeOH)
42		56-58	-92.0 (C=0.3, MeOH)
43		96-98	-40.4 (C=0.5, $CHCl_3$)
44		84-86	-41.3 (C=0.3, MeOH)
45		84-86	-64.0 (C=0.25, MeOH)

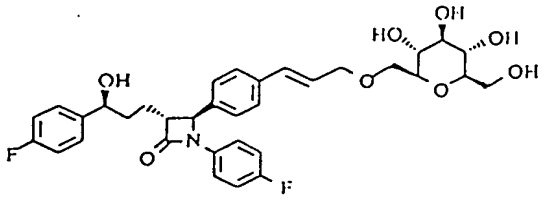
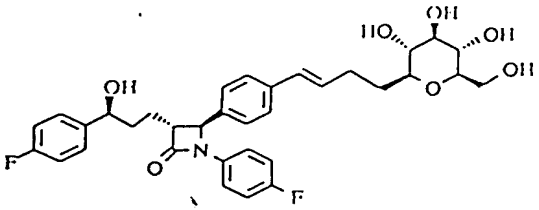
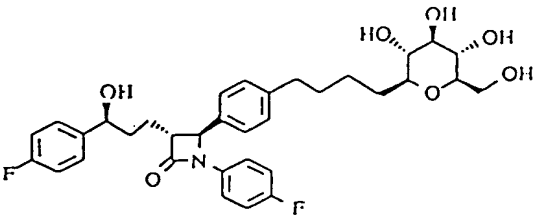
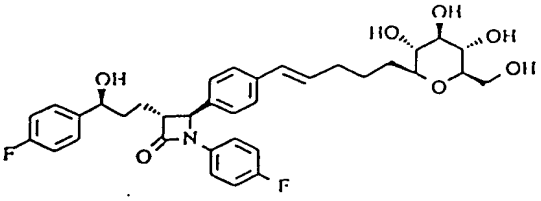
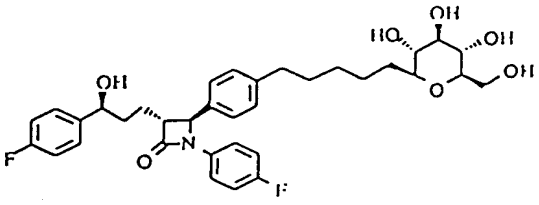
[0025]

[Table 10]

No.	Structure	mp (℃)	$[\alpha]_D^{25}$ / (C, Solv.)
46		153-155	-54.66 (C=0.25, MeOH)
47		72-74	-33.6 (C=1.0, MeOH)
48		81-83	-21.8 (C=1.0, MeOH)
49		111-113	-20.0 (C=0.35, MeOH)
50		61-63	-48.6 (C=0.14, MeOH)

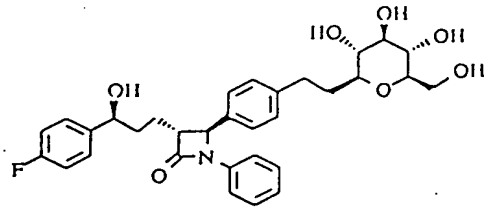
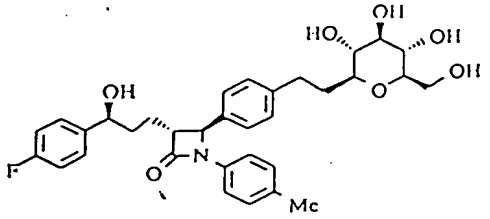
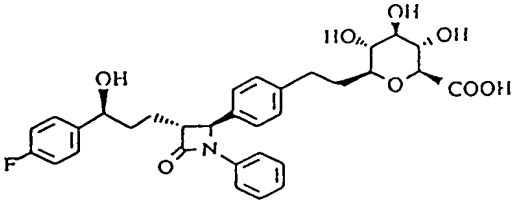
[0026]

[Table 11]

No.	Structure	mp (℃)	$[\alpha]_D^{25}$ / (C, Solv.)
51		65-67	-42.8 (C=0.25, MeOH)
52		79-81	-33.2 (C=1.0, MeOH)
53		81-83	-29.4 (C=0.5, MeOH)
54		69-71	-38.6 (C=0.35, MeOH)
55		66-68	-42.9 (C=0.35, MeOH)

[0027]

[Table 12]

No.	Structure	mp (℃)	$[\alpha]_D^{25}$ / (C, Solv.)
56		82-84	-49.2 (C=1.0, MeOH)
57		116-118	-76.0 (C=0.3, MeOH)
58		110-112	-40.3 (C=0.7, MeOH)

[0028]

Also, cholesterol biosynthesis inhibitors using in the present invention is at least one sort chosen from the group consist of HMG-CoA reductase inhibitors, squalene synthesis inhibitors and squalene epoxydase inhibitors. HMG-CoA reductase inhibitors include, for example, pravastatin, lovastatin, fluvastatin, simvastatin, itavastatin, atorvastatin, cerivastatin, rosuvastatin, pitavastatin and carvastatin (TF802) ; squalene synthesis inhibitors include, for example, squalestatin 1; squalene epoxydase inhibitors include, for example, NB-598 ((E)- N-ethyl -N- (6,6-dimethyl -2-hepten-4-ynyl)-3-[(3,3'-bithiophen-5-yl)methoxy]benzenemethanamine hydrochloride). One or over two agents chosen from those are used in the present invention.

[0029]

Also, fibrate-type cholesterol lowering agents using in the present invention is at least one sort chosen from the group consisting of clofibrate, bezafibrate, simfibrate, fenofibrate, gemfibrozyl and AHL-157.

[0030]

The medicine in the present invention is administered in oral dosage or non-oral dosage form. And, combined usage of a compound represented by the general formula (I) or pharmaceutical acceptable salts and cholesterol biosynthesis inhibitors and/or fibrate-type cholesterol lowering agents can be carried out in various forms. For example, a compound represented by the general formula (I) or pharmaceutical acceptable salts and cholesterol biosynthesis inhibitors and/or fibrate-type cholesterol lowering agents are mixtured at the predetermined ratio, furthermore, it is able to form a combination agents which blended additives and excipients according to the request (a powder agent, a tablet, a granule agent, a capsule agent, a liquid agent, a suspended agent, a suppository, an ointment agent, an inhalation agent and others). Additives and excipients are lubricants, binders, collapses, fillers, buffers, emulsifiers, preservatives, anti-oxidants, coloring agents, coating agents, suspending agents and others.

[0031]

Also, it is able to form a kit by single packaging a container containing a compound represented by the general formula (I) or pharmaceutical acceptable salts and a container containing cholesterol biosynthesis inhibitors and/or fibrate-type cholesterol lowering agents. Also, it is able to administer a compound represented by the general formula (I) or pharmaceutical acceptable salts and cholesterol biosynthesis inhibitors and/or fibrate-type cholesterol lowering agents simultaneously or consecutively.

[0032]

The daily dose of the medicine in the present invention is determined by the potency of the compound administered, the weight, age, and condition of the patient and others. Also, the medicine is administered in a single dose or 2～5 divided doses depending oral or non-oral dosage forms. A compound represented by the general formula (I) or pharmaceutical acceptable salts are administered the amount of 0.1～100mg/kg (mammalian weight) per day by the division. Cholesterol biosynthesis inhibitors are administered the amount of 1mg～3g/kg (mammalian weight) per day by the division, and for HMG-CoA reductase inhibitors are administered the amount of 5～100mg/kg (mammalian weight) per day by the division. For fibrate-type cholesterol lowering agents are administered the amount of 1～1000mg/kg (mammalian weight) per day by the division.

[0033]

[Example]

In the pharmacological experiments of this example, the compound of compound number 56 (called compound 56 as follows) and the compound of compound number 37 (called compound 37 as follows) in the above figure were used as a compound represented by the general formula (I) or pharmaceutical acceptable salts.

Pharmacological experiment 1

The pharmacological experiment of serum cholesterol lowering action by the combination of compound 56 and atorvastatin or fenofibrate.

Male Sprague Dawley rats weighing 300～500g (Japan SLC, Inc.) were fed MF-2 chow (CREA Japan, Inc.)until study onset. At the study onset, the chow was changed to MF-2 chow containing 1% cholesterol and 0.5% cholic acid. Compound 56 at 0.3mg/kg, atorvastatin at 1mg/kg or fenofibrate at 10mg/kg dissolved in polyethylene glycol 400 were simultaneously administered once a day for 7 days. Twenty hours after the last administration, blood was collected from the abdominal aorta under ether anaesthesia, and serum was separated. The cholesterol value was measured using Cholesterol E Test Wako (Wako Pure Chemical Industries. Ltd.). Furthermore, the effect of combined dosage of compound 56 at 0.3mg/kg and atorvastatin at 1mg/kg or fenofibrate 10mg/kg were examined similarly. The results were shown in Table 13. The experimental numbers of 1～3, 4 and 5 indicates the case of compound 56 alone, atrovastatin alone and fenofibrate alone, respectively. The experimental numbers of 6 and 7 indicates the combined dosage examples in the present invention. Each reduction percent of serum cholesterol value is shown as the value to control.

[0034]

[Table 13]

Experimental number	Group	Dose (mg/kg/day)	Number per group	Reduction % of serum cholesterol value
1	Compound 56	0.03	6	1.9
2	Compound 56	0.3	6	6.9
3	Compound 56	1	6	33.5
4	Atorvastatin	1	6	6.2
5	Fenofibrate	10	6	10.7
6	Compound 56 Atorvastatin	0.3 1	6	20.2
7	Compound 56 Fenofibrate	0.3 1	6	41.3

[0035]

From Table 13, in the case of combined dosage compound 56 at 0.3mg/kg/day and atorvastatin 1mg/kg/day (Experimental number 6), and compound 56 at 0.3mg/kg/day and fenofibrate at 10mg/kg/day (Experimental number 7), each reduction % of serum cholesterol value was over the sum of reduction % when each agent was administered alone (Experimental number 2, 4 and 5), indicating synergistic effect.

Pharmacological experiment 2

Except of the use of compound 37 instead of compound 56, complete same experiment as pharmacological experiment 1 was carried out. The results were shown in Table 14. Each reduction % is shown as the value to control.

[0036]

[Table 14]

Experimental number	Group	Dose (mg/kg/day)	Number per group	Reduction % of serum cholesterol value
11	Compound 37	0.03	6	5.6
12	Compound 37	0.3	6	18.0
13	Compound 37	1	6	31.0
14	Atorvastatin	1	6	6.2
15	Fenofibrate	10	6	10.7
16	Compound 37 Atorvastatin	0.3 1	6	31.5
17	Compound 37 Fenofibrate	0.3 1	6	39.5

[0037]

From Table 14, in the case of combined dosage compound 37 at 0.3mg/kg/day and atrovastatin 1mg/kg/day (Experimental number 16), and compound 37 at 0.3mg/kg/day and fenofibrate at 10mg/kg/day (Experimental number 17), the reduction % of serum cholesterol values were over the sum of reduction % when each agent was administered alone (Experimental number 12, 14 and 15), indicating synergistic effect.

[0038]

[Effect of the invention]

The medicine consist of the combination of a compound represented by the following general formula (I) or pharmaceutical acceptable salts and cholesterol biosynthesis inhibitors and/or fibrate-type cholesterol lowering agents show the synergistic effect and an excellent serum cholesterol lowering effect or preventive or therapeutic effect for atherosclerosis. Therefore, it is useful for serum cholesterol lowering or prevention or therapy for atherosclerosis.

[Title of the document]

[Abstract]

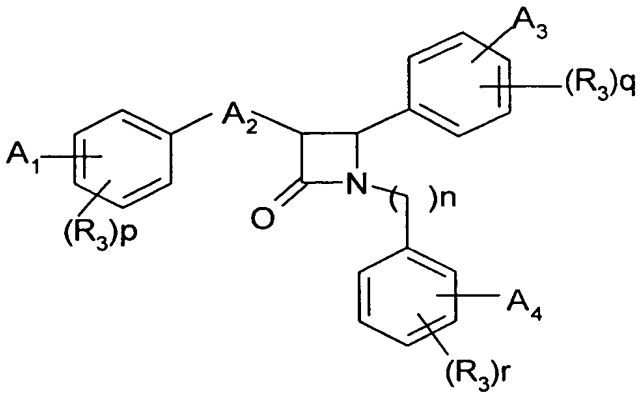
[Problem]

Offering excellent serum cholesterol lowering agents, or preventing or therapeutic agents for atherosclerosis.

[Mean for solving a problem]

Serum cholesterol lowering agents, or atherosclerosis preventing or treating agents consist of the combination of a compound represented by the following general formula (I) or pharmaceutical acceptable salts and cholesterol biosynthesis inhibitors and/or fibrate type hypocholesterolemic lowering agents.

[Compound 1]



---------- (I)

[wherein : A_1, A_3 and A_4 are hydrogen atom, halogen atom, alkyl group having one to five carbon atoms, alkoxy group having one to five carbon atoms, $-COOR_1$, a following formula (b) (wherein : R_1 is hydrogen atom or alkyl group having one to five carbon atoms) or a following formula (a) (wherein : R_2 is $-CH_2OH$ group, $-CH_2OC(O)-R_1$ group or $-CO_2-R_1$ group ; R_3 is –OH group or $-OC(O)-R_1$ group ; R_4 is $-(CH_2)_kR_5(CH_2)_l-$ (k and l are 0 or l more integer ; k + l is 10 or fewer integer). R_5 means single bond (-), -CH=CH-, $-OCH_2-$, -NH-, $-S(O)_m-$ (m are 0, 1 or 2), carbonyl group or –CH(OH)-.)) One of A_1, A_3 and A_4 in formula (I) must be the group in above-mentioned formula (a). A_2 is alkyl chain having one to five carbon atoms, alkoxy chain having one to five carbon atoms, alkenyl chain having one to five carbon atoms, hydroxylalkyl chain having one to five carbon atoms or carbonyl alkyl chain having one to five carbon atoms. n, p, q or r are 0, 1 or 2.]